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Dilute Russell Viper Venom Time: A Useful Assay for the Monitoring of Direct Oral Anticoagulants in Patients?

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Background

Direct oral anticoagulants (DOACs) include anti-IIa agent (dabigatran etexilate) and anti-Xa agents (rivaroxaban, apixaban and edoxaban). DOACs do not require monitoring nor frequent dose adjustment. However, searching for the optimal response at the individual patient level may be useful in some situations. Activated partial thromboplastin time, Hemoclot Thrombin Inhibitor[®] (HTI) and ecarin clotting time have been proposed to monitor dabigatran whereas anti-Xa chromogenic assays are preferable to monitor anti-Xa agents^{1,2,3}. However, there is still a need for a global test easily implementable and widely available that may be used for all DOACs. Recent studies showed that the dilute Russell Viper Venom Time (DRVV-T) could be used for the monitoring of DOACs but these results have not been performed on clinical samples⁴.

Objectives

To analyse and compare the results obtained with STA[®]-DRVV Screen and STA[®]-DRVV Confirm with the plasma drug levels measured by LC-MS/MS.

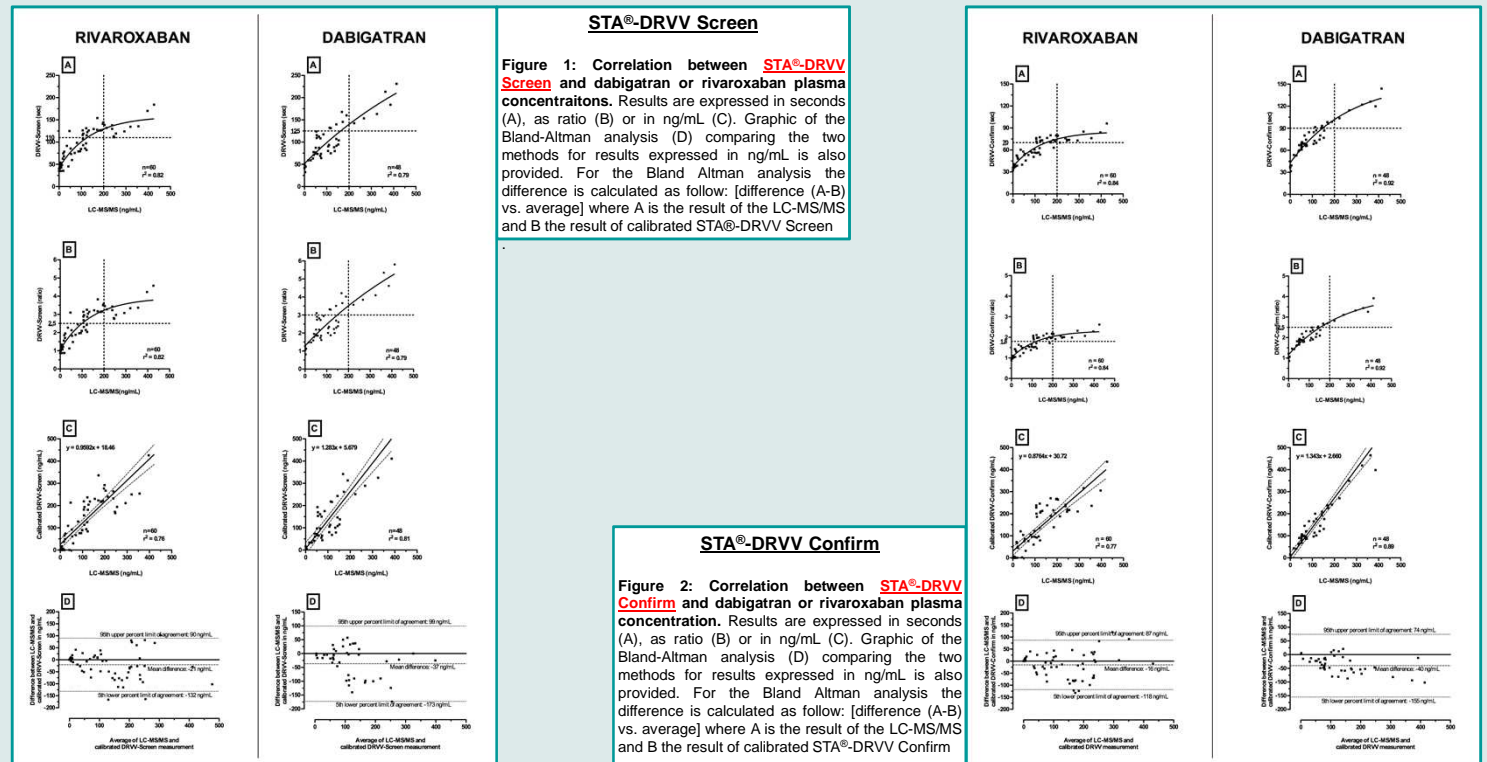
Methods

60 plasmas from patients treated with rivaroxaban and 48 plasmas from patients treated with dabigatran etexilate were included in the study. Plasma concentrations were measured by LC-MS/MS. STA[®]-DRVV Screen and Confirm (Diagnostica Stago[®]) were performed on the 108 plasma samples. All methodologies were performed according to the recommendations of the manufacturer.

Conclusions

- The DRVV cannot be used to accurately estimate dabigatran and rivaroxaban plasma concentrations
- Specific cut-off could however be proposed to rule out excessive concentrations (i.e. concentrations > 200ng/mL at Ctrough)
- However, these cut-offs are specific for dabigatran and rivaroxaban due to difference in sensitivities and also depend on the quantity of phospholipid in the test.

Results



Discussion

The dabigatran plasma concentration ranged from 0 to 413ng/mL and the rivaroxaban plasma concentration ranged from 0 to 426ng/mL.

Correlation between STA[®]-DRVV Screen and LC-MS/MS measurements

Calibrated STA[®]-DRVV Screen and dabigatran or rivaroxaban plasma concentrations correlate well (Figures 1 C). The Spearman correlation is 0.84 (95% CI: 0.72 – 0.91; p<0.0001) and 0.88 (95% CI: 0.82 – 0.93) for dabigatran and rivaroxaban, respectively. When expressed in seconds or as ratios the relation is not linear and is best fit by a second order relation (Figures 1 A & B). Results of the Bland-Altman analysis reveal a mean difference of -37ng/mL and -21ng/mL for dabigatran and rivaroxaban, respectively, with large confidence interval. This implies that STA[®]-DRVV Screen tends to overestimate the concentration of dabigatran and rivaroxaban in plasma samples. Therefore STA[®]-DRVV Screen should not be used to estimate plasma concentrations of both dabigatran and rivaroxaban. However, specific cut-off associated with supra-therapeutic concentrations at Ctrough (i.e. 200ng/mL which represent the 90th percentile of plasma concentrations at Ctrough) could be defined. Thus, a ratio of 2.5 or 3.0 could exclude plasma concentration above 200ng/mL for dabigatran and rivaroxaban, respectively.

Correlation between STA[®]-DRVV Confirm and LC-MS/MS measurements

Calibrated STA[®]-DRVV Confirm and dabigatran or rivaroxaban plasma concentrations correlate well (Figures 2 C). The Spearman correlation is 0.94 (95% CI: 0.89 – 0.97; p<0.0001) and 0.89 (95% CI: 0.82 – 0.94; p<0.0001) for dabigatran and rivaroxaban, respectively. When expressed in seconds or as ratios the relation is not linear and is best fit by a second order relation (Figures 2 A & B). Results of the Bland-Altman analysis reveal a mean difference of -40ng/mL and -16ng/mL with large confidence interval for dabigatran and rivaroxaban, respectively. This implies that STA[®]-DRVV Confirm tends to overestimate the concentration of dabigatran and rivaroxaban in plasma samples. Therefore STA[®]-DRVV Confirm should not be used to estimate plasma concentrations of both dabigatran and rivaroxaban. As for STA[®]-DRVV Screen, specific cut-off could be proposed and a ratio of 1.8 or 2.5 at Ctrough with STA[®]-DRVV Confirm could exclude supra-therapeutic levels of dabigatran and rivaroxaban, respectively.

Disclosure

The authors have no relevant conflicts of interest to disclose.

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